REMARKS

Status of the Claims

Claims 1-38 were pending. Claims 4, 5, 8-10, 12-19 and 22-36 and 38 were withdrawn as drawn to non-elected inventions. Claims 4-5, 7-10, 12-19, 21-36 and 38 are canceled without prejudice or disclaimer, Applicants reserve the right to prosecute the canceled subject matter in a divisional or continuation application. Claims 1-3, 6, 11, 20 and 37 are currently under examination.

Amendments to the Claims

Claim 1 is amended to delete recitation of non-elected embodiments. Claim 1 is further amended to clarify that the antibody comprises antigen-binding variable region domains specific for a cell marker specific to a targeted cell. Support for the amendment may be found in the published Specification (Publ. No. 20040077843) at least at Paragraph [0022], which recites that, "Suitable antibody fragments include $F(ab')_2$, $F(ab)_2$, Fab', Fab, Fv and the like, including hybrid fragments. Also useful are any subfragments that retain the hypervariable, antigen-binding region of an immunoglobulin." Applicants submit that no new matter is added by amendment.

Claims Objections

The Action objects to claims 1-3, 7, 20 and 21 as being drawn to non-elected embodiments. Amendment of claim 1 to delete non-elected embodiments IL-2Rα and IL-15Rα moots the objection.

Rejection of Claims Under 35 U.S.C. §102

The Action rejects claims 1-3, 7, 20 and 21 under 35 U.S.C. 102(b) as anticipated by Konig et al. (Immunology 85:604-10, 1995, hereafter "Konig") as evidenced by Coleman et al. (2003), Guyre et al. (1997) and Seipelt et al. (1997). The Action asserts that Konig teaches a fusion protein comprising the extracellular domain of IL-4R linked to an Fc antibody fragment, and that the Fc portion if IgG is specific for the cell marker CD64.

Although Applicants traverse the rejection, in order to advance the prosecution claim 1 has been amended to clarify that the claimed antibodies or antibody fragments comprise antigen-binding variable region domains specific for a cell marker specific to a targeted cell. That is, it is the antigen-binding variable regions of the antibodies or fragments that provide binding to target cell specific markers, not the constant regions as in Konig. Since this element is missing from the cited Konig reference, rejection of the amended claims under 35 U.S.C. 102 is improper. Reconsideration and withdrawal of the rejection are requested.

Claims 1-3, 7, 20 and 21 are also rejected under 35 U.S.C. 102(a) as anticipated by Seipelt et al. (BBRC 239:534-42, 1997, hereafter "Seipelt"). The Action asserts that, "Seipelt et al. teach a fusion protein comprising the ligand-binding extracellular domain of IL-4Rα linked to an Fc antibody fragment from human IgG." As discussed above, Applicants assert that the element of an antibody or antibodies comprising antigen-binding variable region domains specific for a cell marker specific to a targeted cell is missing from Seipelt and therefore rejection of the amended claims under 35 U.S.C. 102 is improper. Reconsideration and withdrawal of the rejection are requested.

Claims 1-3, 7, 20 and 21 are rejected under 35 U.S.C. 102(e) as anticipated by Enssle et al. (U.S. 6,210,661, hereafter "Enssle"). The Action asserts that, "Enssle et al. teach a fusion protein comprising the ligand-binding extracellular domain of IL-4R linked to an Fc antibody fragment. For the same reasons discussed above, Applicants assert that the amended claims are not anticipated by Enssle and request reconsideration and withdrawal of the rejection.

Rejection of Claims Under 35 U.S.C. §§102/103

Claims 1-3, 7, 20 and 21 are rejected under 35 U.S.C. §102(e) as anticipated by, or under 35 U.S.C. §103(a) as obvious over Willson et al. (WO 97/15662, 1997, hereafter "Willson"). The Action asserts that Willson teaches, "fusion proteins comprising a polypeptide designated NR4 and immunoglobulins that allow targeting of NR4 to particular cells (See entire document, e.g., page 7, lines 15-21, page 10, lines 6-21 and page 11, lines 1-13). The Action further asserts that Willson teaches that NR4 polypeptides include a ligand-binding polypeptide that comprises an amino acid sequence derived from IL-4 receptor alpha.

The cited portions of Willson are reproduced below:

> Other fusion or chimeric molecules contemplated by the present invention include those between NR4 and members of the haemopietin receptor family, receptor tyrosine kinases, TNF/NGF receptors and G protein-coupled receptors. For example, chimeras may be between NR4 and IL- 13 binding protein, IL-4 receptor a-chain, IL-2 receptor y-chain or receptors for other cytokines involved or implicated in asthma and allergy such as IL-5. Other important chimeras include NR4 and immunoglobulins or other molecules which allow targeting of NR4 to particular cells or tissues, NR4 and toxins and NR4 and growth factors. (Willson pg. 7, lines 15-21)
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> Another embodiment provides a method of producing a recombinant polypeptide having at least three of the following characteristics: (i) comprises an amino acid sequence substantially as set forth in SEQ ID NO:2 or SEQ ID NO:4 or having at least about 50% similarity to all or part thereof; (ii) is encoded by a nucleotide sequence substantially as set forth in SEQ ID NO: 1 or SEQ ID NO:3 or having at least about 50% similarity to all or part thereof; (iii) interacts with IL-13 or its derivatives with at least low affinity; (iv) has a molecular weight of from about 50,000 to about 70,000 daltons as determined by Western blot analysis when expressed in COS cells; (v) comprises an amino acid sequence derived from IL-4 receptor a-chain; and (vi) is capable of interaction with IL-13 which is competitively inhibited by IL-4 in cells which express an IL-4 receptor a-chain. said method comprising culturing cells comprising the fusion genetic constructs according to the present invention for a time and under conditions sufficient to express the nucleic acid molecule. (Willson pg. 10, lines 6-21)
>
> As stated above, the present invention further contemplates a range of derivatives of NR4. Derivatives include fragments, parts, portions, mutants, hybrids (including fusion and chimeric molecules), homologues and analogues of the NR4 polypeptide and corresponding genetic sequence. In one preferred embodiment, the derivatives bind IL-13 with high affinity. Other preferred derivatives act as agonists, antagonist or mimetics. Derivatives also include single or multiple amino acid substitutions, deletions and/or additions to NR4 or single or multiple nucleotide substitutions, deletions and/or additions to the genetic sequence encoding NR4.
> "Additions" to amino acid sequences or nucleotide sequences include fusions with other peptides, polypeptides or proteins or fusions to nucleotide sequences. Reference herein to "NR4" includes reference to all derivatives thereof including functional derivatives or "NR4" immunologically interactive derivatives. The present invention also extends to hybrid molecules, such as between murine or human NR4 or derivatives thereof. A particularly preferred hybrid comprises NR4 and IL-4 receptor a-chain. (Willson pg. 11, lines 1-13)

Applicants note that none of the cited passages in Willson disclose any actual fusion protein comprising any antibody or antigen-binding antibody fragment attached to IL-4Rα. At most, at the end of the cited passage from page 7, there is a mere suggestion that a chimeric molecule might

include NR4 and an immunoglobulin. This is merely one suggestion from a list of possible suggestions, including NR4 and a haemopietin receptor [*sic*], NR4 and a receptor tyrosine kinase, NR4 and TNF/NGF receptors, NR4 and G protein-coupled receptors, NR4 and toxins and NR4 and growth factors. No actual working example, showing a fusion of NR4 with any cell-targeting antibody or fragment, is disclosed in Willson. Further, Applicants are unable to find any working example in Willson disclosing a fusion protein comprising NR4 and a cell targeting molecule. At most, Example 12 shows a fusion of NR4 with the short FLAG epitope sequence used for protein purification.

Applicants respectfully submit that the reference of Willson is a classic "obvious to try" rejection, with no actual disclosure of any species within the claimed subject matter and little or no guidance provided to the skilled artisan on how to make and use an NR4-immunoglobulin fusion protein. Only the first recited passage of Willson even mentions the possibility of an immunoglobulin comprising fusion protein (among 6 other possibilities). The second cited passage concerns the incorporation of an IL-4Rα derived sequence in NR4, and the third cited passage merely states that (unspecified) fusion proteins and chimeric molecules are contemplated.

Applicants respectfully submit that Willson does not provide an enabling disclosure of IL-4Rα attached to a cell-targeting antigen-binding antibody or antibody fragment, as required to support a prior art rejection under MPEP §2121.01.

None of the cited prior discloses any species within the scope of the claimed subject matter. Willson at most provides a mere invitation to experiment with the production of a large number of possible fusion proteins comprising NR4, with no guidance to the skilled artisan of what antibodies or antibody fragments might be of use to make such a fusion protein. With that lack of guidance, and nothing in the way of working examples, Applicants submit that there could have been no reasonable expectation of success in making and using the claimed invention, based on the disclosure of Willson in combination with other cited art or with general knowledge in the field. In the absence of a reasonable expectation of success, a prima facie case of obviousness has not been established under MPEP §2142 and rejection under 35 U.S.C. 103 is improper. Reconsideration and withdrawal of the rejections are respectfully requested.

Rejection of Claims Under 35 USC § 103(a)

Claims 1, 6, 11 and 37 are rejected under 35 USC § 103(a) as being unpatentable over Willson (1997), in view of Hu et al (Cancer Research 56:4998-5004, 1996; hereafter "Hu"), Fritzberg et al. (U.S. 5,976,535, hereafter "Fritzberg") and Schwarz et al. (Cancer Res. 55:3692-96, 1995, hereafter "Schwarz").

The deficiencies of Willson are noted in the section above, incorporated herein by reference. Applicants reiterate that Willson fails to provide any enabling disclosure relevant to a fusion protein comprising an antigen-binding antibody or fragment attached to IL-4Rα. That deficiency is not made up for in any of the other cited references. Hu is asserted to teach, "a targeting moiety comprising a fusion protein of the Lym-1[2] [i.e., anti-HLA-DR] antibody linked to IL-2, targeting IL-2 to lymphoma cells. Fritzberg is asserted to teach moieties comprising antibodies specific for a target cell conjugated to one member of a ligand/anti-ligand pair, such as streptavidin-biotin, for targeting tumors with anti-tumor agents such as IL-4. Scharz is said to teach use of IL-4 to reduce tumor burden. Rolling is said to show that IL-4Rα is identical to IL-13Rα.

According to the Action, Hu and Fritzberg are asserted to disclose attachment of targeting antibodies to IL-2 or IL-4, not to IL-4Rα. If anything, Hu, Fritzberg and Scharz teach away from the claimed subject matter, by leading the skilled artisan to believe that antibodies or fragments should be attached directly to interleukins, not to an interleukin receptor protein. The skilled artisan, reading Hu, Fritzberg and Scharz would be lead to believe that targeted tumor therapy should be based on administration of interleukins themselves, not on their receptor proteins.

Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

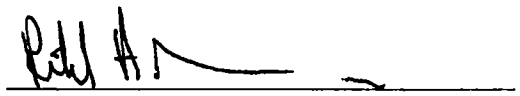
The Action rejects claims 1-3, 7, 20 and 21 on the grounds of nonstatutory obviousness-type double patenting over claims 1-13 of U.S. Patent No. 6,703,488 as evidenced by Rolling.

Applicants respectfully traverse the rejection. However, in the interests of advancing prosecution, a terminal disclaimer will be submitted when otherwise allowable subject matter has been found in the instant application.

CONCLUSION

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance.

Respectfully submitted,



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